

Af



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,424	12/28/2000	Adrian Auf Der Maur	27656/37021	7858
4743	7590	02/03/2006	EXAMINER	
MARSHALL, GERSTEIN & BORUN LLP 233 S. WACKER DRIVE, SUITE 6300 SEARS TOWER CHICAGO, IL 60606			WESSENDORF, TERESA D	
			ART UNIT	PAPER NUMBER
			1639	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/750,424	Applicant(s) DER MAUR ET AL.	
	Examiner T. D. Wessendorf	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31,33-38 and 42-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31,33-38 and 42-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

Claims 31, 33-38 and 42-47 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 31, 33-38 and 42-47, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A). *New Matter*

The claimed "irrelevant antigen specificity" is not supported in the as-filed specification. Applicants state that support can be found at page 16, line 24 up to page 17, lines 6 and Figs. 1 A and B. A review of e.g., page 17, lines 6-15 does not support the present phraseology. Page 17 states ".....present invention was demonstrated using a number of well characterised scFvs. These possess essentially identical antigen binding properties but different in vitro stabilities...." Figs. 1 relate

Art Unit: 1639

to specific intrabody fusion with Gall1P-Gal4. See also claim 19, step © which presupposes the specificity reaction of antigen/intrabody inorder for the cell to grow or survive.

The new matter rejection that the claimed "soluble and stable in ***selected conditions***" is not supported in the as-filed specification has not been responded to. In the absence of any response, it is believed that applicants are acquiescing therewith.

B). *Written Description*

In view of applicants' arguments, the lack of written description under 35 U.S.C. 112, first paragraph is withdrawn.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 36 which recites that identifying cells expressing a first and a second protein interacting with each other via a constant region of the first protein. The specification recites for a library for the constant region of the first protein. Cf. with the specification, page 34, line 31 up to page 19, line 18. Also, see the Examples.

Applicants have not responded to this objection. Since applicants have not responded to this objection, hence, it is believed that applicants are acquiescing therewith.

Claim Rejections - 35 USC § 102

In view of applicants' arguments, the rejection of the claims under 35 U.S.C. 102(b) as being anticipated by Visintin et al (PNAS) is withdrawn.

Claims 36-38 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoffler et al (US 20030017149) for reasons advanced in the last Office action.

The response below under Visintin is incorporated herein since applicants argue same rejections for Hoeffler and Visintin.

Claim Rejections - 35 USC § 103

Claims 31, 33, 35-38 and 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin et al (PNAS) for reasons set forth in the last Office action.

Response to Arguments

Applicants argue that Visintin relied upon the use of the two hybrid system for the isolation of intrabodies using an antibody/antigen interaction and do not determine whether an intrabody is soluble and stable as recited in claim 19. Visintin assays give a positive signal if an intrabody is soluble, stable and specific for the target antigen and do not give a signal

Art Unit: 1639

(they report a false negative) when the intrabody is soluble and stable but is not specific for (lacks binding affinity for) the target antigen.

In response, it is sufficient that Visintin discloses that the intrabody is soluble and stable under the selected conditions that interact with the antigen. It is not necessary that Visintin provides a signal if the intrabody is not specific for an antigen, since the claims do not recite any false negative or positive signal. The claims do not differentiate what is a positive or negative signal. What is required, as applicants seemed to admit, is that the intrabody is soluble and stable under the reducing environment. Visintin performs simultaneously the solubility, stability and antigen interaction. The claims performed the same steps in separate determinations, steps (a) and (b). Step (b) claims that antigen interaction is determined for the soluble and stable intrabody. Visintin, like the instant claims, employs a marker to determine the stability and solubility of the antigen. Neither Exhibit A nor B is shown in the as-filed specification and for the reasons above does not overcome the rejection.

Applicants argue that Visintin fails to disclose the detection methods of the application wherein the detection of the marker protein is not dependent upon the presence of an

Art Unit: 1639

antigen for which the intrabody is specific, it would not have been obvious to modify Visintin in the manner claimed. This is because Visintin Fig. 1 describes an "antibody-antigen ... interaction assay" and relies upon the occurrence of an antigen-antibody interaction to perform its assay. Thus, in the absence of an antigen-antibody interaction the Visintin assay would be susceptible to providing falsely negative results regarding the stability of the intrabody framework because of the failure of antigen-antibody binding. Specifically Visintin relies upon the use of the two hybrid system for the isolation of intrabodies using an antibody/antigen interaction wherein the claimed identification of the intrabodies is based on the antigen dependent interaction between the antibody and its corresponding antigen. An examination of Figure 1 of Visintin et al. shows that the two-hybrid method was adapted "to detect antibody-antigen interaction in vivo." I[f] the antibody-antigen interaction occurs in vivo, the resulting complex can bind to the LexA DBS upstream of his or lacZ genes resulting in either growth of the transformed yeast or expression of a visible signal respectively. A comparison of Figure 1 of Visintin with Applicants' Figure 1 is solicited.

In reply, the claims specifically, steps ©-(e) also recite antibody-antigen interaction for the assay. The preamble recites

Art Unit: 1639

"screening for intrabodies with CDRs interacting with a specific antigen". How else will one determine whether an intrabody is soluble and stable but to react it with an antigen? At page 11723, col. 1 and col. 2, Visintin states that when antibodies are expressed in the cell cytoplasm, folding and stability problems often occur resulting in low expression levels and limited half-life of antibody domains. These problems mostly are caused by the reducing environment of the cell cytoplasm, which hinders the formation of the intrachain disulfide bond of the VH and VL domains and is important for the stability of the folded proteins. Visintin recognizes that there is a need to obtain antibody fragments that will fold and are stable and soluble under conditions of intracellular expression. The two-hybrid system (which is the same as used in the instant disclosure) is used to monitor intracellular antigen-antibody interactions via reporter gene activation. The use of reporter assays to detect antibody-antigen interaction in vivo thus provides a strategy to select those individual antigen-specific scFv that can function in cells. Visintin at page 11726 states that the use of the two-hybrid assay for intracellular antigen-antibody interactions should allow the isolation of antibody domains that tolerate the absence of the intra-chain disulfide bond in the reducing environment of the cytoplasm. Many of these intracellular do not

Art Unit: 1639

function inside cells. At page 11727, col. 2 Visintin states that the paucity of functional intracellular scFv requires selection procedures that are based on intracellular action rather than in vitro antigen binding alone. The two-hybrid assay is a general assay that depends upon that the interaction of scFv with antigen under intracellular conditions. Because under intracellular conditions the antibody is unstable and not soluble. The folding stability of antibody domains are contributed by many residues in the frameworks with different scFv fragments having different overall stabilities. Good intracellular expression is related to additional parameters such as solubility versus propensity to aggregate, cellular half-life and others. The in vivo selection scheme for the isolation of intracellular scFv, based on their ability to bind antigen under conditions of intracellular expression would presuppose that the scFv should be soluble and stable since if not under the intracellular conditions it would not bind to antigen.

Applicants argue that the Visintin assay will give a positive signal if an intrabody is soluble, stable and specific for the target antigen, it will not give a signal (it reports a false negative) when the intrabody is soluble and

Art Unit: 1639

stable but is not specific for (lacks binding affinity for) the target antigen.

In response, applicants' arguments are not commensurate in scope with the claims. The claims do not recite that a signal is produced when the intrabody does not react with antigen but is stable and soluble. The claims steps ©-(e) recite that the cells containing the intrabody-antigen grow, meaning that the specificity reaction is required to establish that the intrabody is soluble and stable. Attention is again drawn to page 11727, Discussion section of the Visintin reference. Visintin discloses that the many residues in the frameworks with different scFv fragments have different overall stabilities. Visintin tested those that are stable and the stable ones are then tested for antigen specificity. Thus, the suggested teachings of Visintin concerning the stability of intrabody and tested only the stable ones would indicate that he assayed the solubility and stability intrabody prior to antigen reaction. Whether it gives a positive signal or not is irrelevant to the finding of obviousness as to the determination of a soluble and stable intrabody, as the claims do not provide said differentiation.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin above in view of Ptashne et al (20040014036) for reasons of record.

Response to Arguments

Applicants argue only Visintin as indicated above and did not present arguments over the combined teachings of Visintin and Ptashne. In the absence of such response, it is believed that applicants are acquiescing to the rejection of claim 42 over the combined teachings of Visintin and Ptashne.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin as applied to claims 31, 33, 35-38 and 43-47 above, and further in view of Martineau (J. Mol.Biol.) or Nolan et al (USP 6,153,380) for reasons of record.

Applicants did not response to the collective teachings of the prior art. In the absence of such response, it is believed that applicants are acquiescing to the rejection of claim 34. However, the response to Visintin is discussed above.

Double Patenting

Claims 31, 33-38, 43-47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23 and 39 of

copending Application No. 10/169,179('179 application) for reasons of record.

Response to Arguments

Applicants urge deferring this rejection until an indication of allowable claims in both applications are made. At that time applicants will consider the allowable claims of each case and either submit arguments that the claims are unobvious over each other or submit a terminal disclaimer.

In response, in the absence of a terminal disclaimer, the rejection is maintained.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will

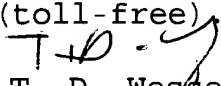
Art Unit: 1639

expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw

February 1, 2006